Exhibit F

March 1, 2016

Expert Report of Shelby F. Thames, Ph.D.

Prepared for

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF WEST VIRGINIA
CHARLESTON DIVISION

IN RE: ETHICON, INC., **PELVIC REPAIR SYSTEM PRODUCTS** **LIABILITY LITIGATION**	**Master File No. 2:12-MD-02327** **MDL 2327** **JOSEPH R. GOODWIN** **U.S. DISTRICT JUDGE**
THIS DOCUMENT RELATES TO: *Wave 1 Cases*	

I have been asked to analyze Ethicon's Prolene, the mesh material at issue in this medical device, and offer opinions concerning claims that the mesh used in Ethicon's product is not suitable for implantation. I have analyzed several other claims involving Ethicon's mesh devices used for the treatment of stress urinary incontinence and pelvic organ prolapse. Accordingly, I have included in this report my analyses of some of these products. I have also included in this report critiques of other expert reports offered in other cases in which Ethicon's mesh products have been at issue.

Ethicon's mesh product is made of Prolene mesh. Prolene is the Ethicon brand name for its mesh material. Chemically, Prolene consists of polypropylene plus the addition of five highly proprietary additives as discussed herein. Where I refer to polypropylene used in Ethicon's mesh, I am referring to the specific polypropylene and proprietary additives that make this mesh different from mesh marketed by other manufacturers. All my opinions herein are offered to a reasonable degree of scientific certainty.

I have been asked to do the following:

Response to Dr. Jimmy W. Mays Report

I have reviewed Plaintiff's expert report and have the following comments.

Plaintiff' data is included herein as the Imel, Malmgren, Dadmun, Gido and Mays 2015 Biomaterials manuscript which has been cited herein several times.[296] In drawing conclusions the works of Mary, Clavé, Liebert, Costello, Ostergard, Bracco, and Iakovlev in particular, have been cited. With the exception of Bracco, I have responded to the writings of the remaining authors, in this and other reports, but will add additional comments herein. Several references deal with ethylene oxide containing polyurethanes and the authors attempt to relate polyurethane (PU) chemistry to Polypropylene (PP) chemistry, although they are completely different polymer types. Moreover, those reading these reports should be reminded Prolene, i.e. PP formulated with 5 additives, is the focus of this litigation, and not PP.

Plaintiff's expert report included a statement of purpose and it is, "This report focuses on the following key issues:

- the chemical structure and properties of polypropylene,
- degradation of polypropylene by thermo-oxidative processes *in vivo*
- and effects of *in vivo* degradation on the polypropylene implant."

I will comment by providing a response to statements or issues with which I have scientific concerns, i.e.

The first statement of opinion is problematic, i.e. "It has been well understood for many years that polypropylene is susceptible to oxidation and it degrades by an oxidative mechanism in the body, resulting in chain scission and diminished mechanical properties (reduced compliance and brittleness). These facts are clearly documented in the peer reviewed scientific literature."

Response: It is known that Polypropylene will oxidize under specific reaction conditions, i.e. high temperatures in oxygen or air. In fact, my report includes Thermogravimetric data confirming this precept. Indeed, high temperatures are required, i.e. 333.83 ^{o}C or 632.9 ^{o}F and the process is not immediate. It is also well known that PP will oxidize in ultraviolet light (UV).[297] However, UV light is not a degradation issue with Prolene mesh given placement loci. There is, to my knowledge, no acceptable scientific data confirming Prolene degradation in the body, in general, and specifically by an oxidative mechanism. There is no reliable data of which I am aware affirming Prolene's *in vivo* carbonyl groups formation, concomitant with chain scission, molecular weight loss, and loss of physical properties.

As an example, the often referenced article of 1976 is fraught with misinterpretations.[298] Liebert purchased polypropylene pellets, added UV stabilizers of his choice to a portion of the PP, and extruded two PP samples for study; one was formulated with UV stabilizers and one without UV stabilizers.

The fibers were implanted subcutaneously in hamsters in order to determine their *in vivo* rate of degradation. Specimens were removed periodically and analyzed by infrared spectroscopy and dynamic mechanical testing. However, FTIR is not a quantitative technique unless FTIR absorption vs. concentration are first established and his article made no mention of this having been done. Consider the following quote, "Although the reaction sequence is not known, several factors suggest that the *in-vivo* degradation process is similar to autoxidation which occurs in air or oxygen." Thus, in 1976 Liebert and colleagues launched an experimental program with unstabilized PP, without sufficient quantitative analytical tools, and having no

knowledge of the reaction sequence they were to study. Therefore, the Liebert reaction rate data for un-stabilized PP is suspect and conclusions drawn therefrom are of suspect.

The following quote by Liebert is significant and consistent with my work, i.e. “No change in the infrared spectra or tan delta (glass transition temperature) was observed, however, for implants containing an antioxidant.” Liebert is emphatic that there was no change in the FTIR of stabilized PP, no carbonyl groups were produced, no aldehyde groups were produced, no peroxide groups were produced, no change in mechanical properties or infrared spectra were observed for any of the filaments containing antioxidant, etc.. No change simply means no change.

Plaintiff’s expert speaks to the issue of Disproportionation as a primary termination mechanism in the accepted mechanism for PP structural degradation leading to the formation of aldehydes, ketones, and carboxylic acids, with accompanying chain cleavage. However, he was unable to show formation of aldehydes, ketones and carboxylic acids derived from Prolene in his work, i.e. Liebert states, “No change in the infrared spectra or tan delta was observed, however, for implants containing an antioxidant.” Liebert was able to show PP formulated with antioxidant did not undergo oxidative degradation. Yet he is often cited for supposedly confirming oxidative degradation of PP. And thus, the myth continues. There are those who will conveniently ignore Liebert’s stabilized PP data, and seize on his unstabilized PP data. Ethicon does not sell nor promote products of PP without first formulating it into Prolene with five additives, two of which are highly efficient antioxidants.

Plaintiff’s expert writes that salts and enzymes in the body can catalyze degradation and specifically speaks to carbonyl group formation in PP. However, the reference used to support this concept discusses the use of body salts and enzymes leading to the degradation of polymers containing carbonyl groups and PP structure does not possess carbonyl groups. Consequently, this reference or statement has no merit in this matter but serves only to confuse those unfamiliar with organic chemistry and polymer science. Simply put, Prolene does not possess carbonyl groups and therefore, the proposed degradation reaction is inconsistent with its chemical structure.

Plaintiff’s expert has suggested “strong oxidants such as hydrogen peroxide and hypochlorous acid” are produced as a product of a foreign body response function which may attack PP and cause structural damage. However, I am unaware of sound scientific data confirming hypochlorous acid attack on Prolene. For instance, Dr. Peter Moy placed Prolene fibers in 30% hydrogen peroxide for one year, and reported no chemical attack on Prolene.[299] Yet, he noted at the conclusion of this experiment, hydrogen peroxide chemically destroyed the bottle top made from a phenolic polymer laying on its side and in constant contact with hydrogen peroxide, as was Prolene. Furthermore, it is suggested that the body secretes highly reactive oxidizing species (ROS) present on the surface of the implant. The suggestion is ROS’s generated are more sever oxidizing agents than peroxide or hypochlorous. However, I am unaware of credible scientific data that will confirm this thesis.

Plaintiff’s expert has referenced Postlethwait who implanted PP sutures in the abdominal wall muscles of rabbits and recovered specimens over intervals of 6 months to 5 years.[300] The author’s conclusions are “Although in most operations these minutiae of tissue reaction concerning polypropylene are of little consequence, it may be necessary to conduct further studies to determine if they have any significance.”

Plaintiff's expert references 1986 work of Jongelbloed and Worst who examined PP surgical sutures (supplier not identified) that resided in a human eye for 6.5 years. However, as noted earlier in this report, Prolene mesh is not subject to UV radiation by virtue of its placement. It is interesting the investigators used only SEM to examine explants but did not include reference to an FTIR, which could have provided helpful data for determining the explant composition.

Plaintiff's expert's reference Mary once again, i.e. C. Mary, Y. Marois, M. W. King, G. LaRoche, Y. Douville, L. Martin, and R. Guidoin, "Comparison of In Vivo Behavior of Polyvinylidene Fluoride and Polypropylene Sutures Used in Vascular Surgery", ASAIO Journal, 199 (1998)). Several proponents of Prolene *in vivo* degradation reference this work but seem to miss, or choose to disregard, very important scientific principles.

Mary, Et al. uses ATR-FTIR and chooses the lone frequency of 1740 cm^{-1} to confirm Prolene oxidation. The authors write in the manuscript, "both pure polymers (meaning Prolene and PVDF) are devoid of this functional group," meaning the carbonyl group(s) of Ethicon's DLTDP with an absorption frequency of 1740 cm^{-1}. Thus, Mary and her colleagues were unaware of the compositional makeup of Prolene. Consequently, their lack of understanding of the chemical composition of materials evaluated reflect poorly on the quality of their data and its interpretation. This is a classical example of a peer reviewed article possessing significant fundamental errors and finding its way into scientific/medical literature. Even though, given this fundamentally grievous error, her work continues to be cited in peer reviewed articles and important reports as it is herein.

Furthermore, an example of incomplete but otherwise powerful and important information could have easily been obtained by securing elongation values with tensile strength data. While tensile data was reported, elongation values were non-existent therefore toughness values could not be determined.

Aside from the erroneous FTIR data, Mary also used a rigorous preparation and cleaning protocol for the SEM samples in that they were:

- fixed in glutaraldehyde solution, rinsed in distilled water, and post fixed with osmium tetroxide.
- Drying was affected by immersion in ethyl alcohol solutions, followed by critical point (-70 deg. C) using liquid carbon dioxide (this process alone would almost certainly generate artifacts, i.e. cracking).
- Specimens were coated with sputtered gold palladium and viewed by SEM.
- This "fixation" and "drying" process is very rigorous and would produce a brittle material especially during the carbon dioxide critical point drying process. Any movement of the sample would shatter or break surface materials. Yet they speak to the issue of viewed cracks and presumably subscribe them to mesh deficiencies, giving no consideration to high probability of sample preparation artifacts.
- Mary and colleagues base their opinions in part on Liebert, stating he found PP oxidation to carbonyl groups, chain scission, and oxidation within a few days after implanting in rats. What these authors do not say is extremely important to the scientific community; that is, Liebert used PP without UV absorbers and antioxidants, but when UV absorbers were part of the PP formulation, no Prolene degradation of any kind was noted. Mary, Et al. omission of these critical data have served to continue to propagate misinformation via the peer review process.
- Neither have plaintiff's experts made these important scientific facts known but simply continue to reference the flawed Mary work as we see in the present instance.

- Costello, in a similar fashion, continues to be referenced in peer review manuscripts yet he and colleagues gave no consideration to tissue "fixation in Formalin."
- "Fixation" is a chemical crosslinking reaction between formaldehyde and proteins, and typically takes place in the surgery suite when the surgeon explants mesh and places the explanted flesh into a Formalin solution. The fixation reaction continues for an extended period while immersed in formalin. The fixation product is a rigid, hard, insoluble, porous, and brittle; the chemistry of "Fixation" was described more than 50 years ago, and is thoroughly discussed in the chemical literature, and used extensively in medicine for more than 50 years. For instance, see Dr. Susan Lester's Manual of Surgical Pathology.[301] The manual is a treatise said to be in most surgical suites in North America. Dr. Lester discusses fixation thoroughly, and several of her topics deal specifically with issues in this litigation.
- "Fixation in Formalin" simply cannot be ignored. The Formaldehyde-Protein polymer formed during the fixation process must be removed from explants prior to their testing.
- Those who ignore this well know, established, chemical and polymer science precept cannot hope to understand the magnitude of its influence.
- Bracco, in the peer reviewed manuscript, titled Comparison of Polypropylene and Polyethylene terephthalate (Dacron) meshes for abdominal wall hernia repair: a Chemical and Morphological Study state "For the first time, by scanning electron microscopy (SEM), polypropylene (PP) excised meshes (ethylene oxide sterilized) for abdominal wall hernia repair have been shown to be greatly damaged physically,…." PP or PET mesh were fixed in 4% formalin. Bracco then writes "in order to eliminate any organic residue, the fragments were treated for 24 h with NaCl solution (Fluke 6-14% active chlorine) at 37 ^{o}C and washed with distilled water. These fragments were extracted for 24 h with boiling cyclohexane. The extracting cyclohexane was removed with a rotating evaporator and the residue recovered in a few drops of hexane." At this point, explanted mesh has been fixed in formalin, and extracted with cyclohexane. Thus the "Formaldehyde Fixation" process has been performed and the hard, brittle, insoluble, composite formaldehyde-protein polymer has formed. It is not removed by cyclohexane due to its insolubility in this non-polar, hydrocarbon solvent. To further complicate SEM analyses, the samples were sputter coated with gold "in preparation for SEM analysis."
- The sample having been prepared for SEM analysis is without plasticizing agents, encased in a formaldehyde-protein composite polymer and made even more rigid by sputter coating in gold. This PP material can be viewed in Bracco, Fig.2 and Fig. 3. The explant mesh manufacturers were not identified.
- The explants were insufficiently cleaned, i.e. soaking in sodium hypochlorite solution for 2 hours at 37 ^{o}C followed by rinsing with distilled water is an insufficient cleaning protocol for explanted mesh.

In all the PP excised mesh fragments listed in Table 1 (Fig. 24 and Fig. 25), independently of the manufacturer or the implantation time, the filaments appear badly damaged. This seems to be in disagreement with what is clinically observed [11, 12], namely that PP meshes give an inflammatory response and an extraneous body reaction less than the PET ones. Bracco, like many others, has, for whatever reason, given no consideration to formalin fixation and the resulting formalin-protein polymer. The strongly adhered proteins, and their subsequent reaction with formaldehyde readily accounts for the images of Fig. 24 and 25. This represents yet another peer reviewed article that did not properly consider the Formalin Fixation process.

Thus, the photomicrograph from Costello (Figure 26) is precisely what one would expect of an improperly cleaned explant. Bracco makes specific reference to his Figures 25 when

postulating a primary cause of the cracked and degraded morphology was absorption of small organic molecules of biological origin.

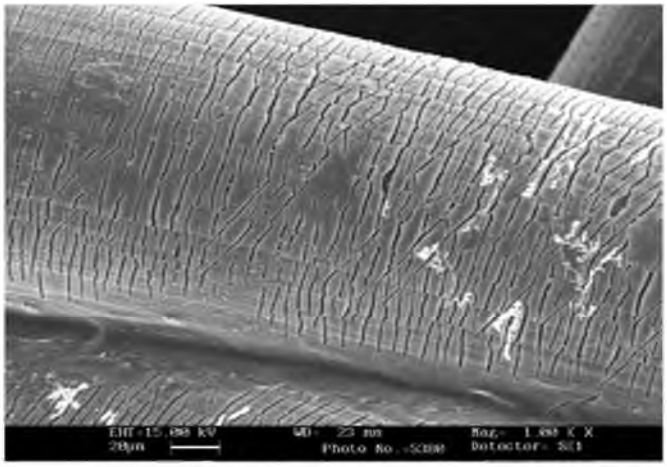

Fig. 3 Scanning electron microscopy (SEM) micrograph (1,000×) of fragment #9 polypropylene (PP)

Figure 24: SEM Image of explanted PP fiber from Bracco (Figure 3)[302]

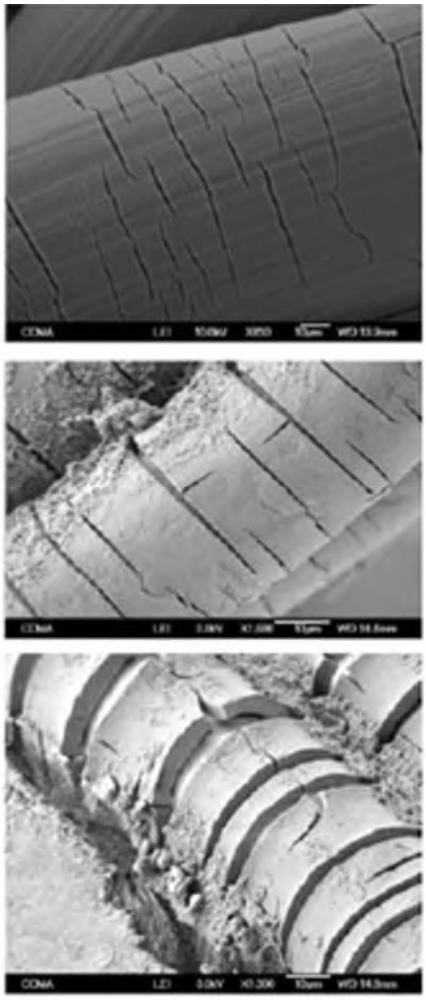

Figure 25. SEM of Transverse Cracking in Explanted PP Fibers from Clavé (Figure 4)[303]

Figure 26 is plaintiff's expert reference to Clavé, et al who reported PP mesh damage as "superficial degradation." Figures 24 and 252 are classical for explanted mesh with essentially no protein removal from PP fiber(s). It is a simple matter to perform an FTIR analysis on samples similar to shown in Figures 24 and 25 to confirm the proteinaceous nature of the protective sheath formed around the PP fiber. We have done so in our labs and, of course, confirmed the composite sheath is of proteinaceous composition, not PP. The proteinaceous composite is formed during the fixation process in formalin.

Plaintiff's expert, Costello, Bracco, Mary, LeFranc, Clavé, and others are a stable of literature contributors who have, and perhaps unknowingly, become part of the misinformation world of PP mesh and its *in vivo* performance. None seem to have recognized and/or appreciate the significance of fiber or mesh "Fixation in Formalin." Consider now Lefranc who included Clavé's photomicrograph (Figure 25.9) of "Degraded PP Mesh." It is obvious even to one not skilled in the art, material(s) possessing surface cracks of the order of magnitude as shown in Fig. 25.9 would expect massive cracking, crack propagation to fiber rupture, and total loss of mechanical properties.

Fig. 25.9 SEM observation of degraded PP mesh under septic environment

Figure 26. Clavé Figure 25.9[304]

Plaintiff's expert has written "It is likely that an increase in free volume of the amorphous regions of implanted PP fibers due to plasticization from the absorption of small, biological organic molecules facilitates increased penetration into the PP fibers by oxygen and other oxidizing chemical species, thus accelerating PP fiber degradation due to oxidation." This is speculation without scientific foundation.

Plaintiff expert references his work with the publication "In Vivo oxidative degradation of polypropylene mesh." I question the statement "It is now well-known that strong oxidizing agents such as hypochlorous acid and hydrogen peroxide are generated as byproducts of the inflammatory response of the body to an implant, and these agents can degrade and embrittle polypropylene, with a loss of flexibility due to oxidation selectively removing the less dense amorphous regions of the material." It is the underscored portion for which I have seen no credible, conclusive scientific data to confirm "these agents can degrade and embrittle polypropylene, with a loss of flexibility due to oxidation, ---."

Imel and Mays, using Boston Scientific mesh, published their work with the intent to "test whether or not oxidative degradation is responsible for observed changes in the mesh upon implantation." They chose analytical tools such as FTIR, SEM, TGA, GPC, and TEM by which to collect data. However, only 4 of 11 samples "were cleaned of residual biological material by soaking 24 h at room temperature in sodium hypochlorite solution (7.85% available chlorine), followed by rinsing extensively with water and drying in a vacuum oven at room temperature." This cleaning technique is insufficient to insure all "fixed proteins" are removed from the Boston Scientific Explants, thus casting doubt and speculation on data collection and opinions therefrom.

Moreover, the display of data is inferior, particularly with FTIR. The authors write "Clear signs of oxidation are seen in the FTIR spectra of all four implants as evidenced by broad peaks centered around 3400 cm^{-1} (hydroxyl and peroxide) and between 1700 and 1750 cm^{-1} (carbonyl)." However there are no frequency displays for the spectra confirming peak assignments.

The TGA data of Fig. 3, page 133, shows the most thermally stable sample tested to begin weight loss at less than 300^{o}C (samples of Fig. 3A) and less than 250 ^{o}C for Fig. 3B. Weight loss for Prolene begins at approximately 333^{o}C.

SEM data and assignments are suspect and misleading given sample preparation, SEM photomicrographs, and data conclusions. Consider the following from the Imel, Mays article:

1. "However, SEM and EDS was performed on all 11 samples."
2. "The explanted samples were contained in jars of formalin solution." This confirmed explant fixation in n Formalin.
3. Explanted samples were rinsed in ultrapure (deionized) water and then allowed to air dry. After drying, the explanted samples were mounted on aluminum SEM sample holders with double sided, conductive tape.
4. "In the preparation for SEM testing sample XP-11 and only XP-11 was treated with sodium hypochlorite solution for removal of biological tissue using the published procedure of Bracco" (See Fig.4, sample C)

Given these data and SEM photomicrographs of the report it is obvious explant samples were not properly/thoroughly cleaned and formaldehyde fixed proteins from flesh remains on the explants. For instance, formalin fixed flesh can easily be seen in Fig.4, C, D, E, and F; Figure 5, A, B; Fig. 6, A, B, C and D; Fig. 7, A, D, E, and F.

The authors set out to use EDS data for the following purpose, "EDS was used to look for the presence of oxygen in polypropylene fibers, which would indicate that degradation due to oxidation has occurred." It is clear the authors do not realize tissue remains on the explants noted above, or they wish to ignore its presence. Viewing Fig.1, A is a Pinnacle Control while B

is an Obtyrx Exemplar control and in the lower section of Fig. 1 EDS spectra, E and F, are controls, yet they show the presence of Carbon and Oxygen. Surely the controls are not oxidized, and that EDS data for both show presence of Oxygen defeats their thesis for confirming oxidative degradation by EDS. The SEM photomicrographs confirms residual flesh, and given all samples were fixed in formalin, all explants are expected to possess, at the very least, Carbon, Hydrogen, Oxygen and Nitrogen. Nitrogen, however, is difficult to analyze by EDS and there may be times when Nitrogen is present but it is not shown on a corresponding EDS spectra.

The GPC data is likewise suspect given the authors did not consider small molecule absorption of Prolene. The absorbed, low molecular weight materials would be eluted through the GPC column, as would higher molecular weight polymer fractions, and in so doing impact the molecular weight data. Bracco clearly confirmed the presence of low molecular weight chemicals via his extraction/FTIR technique.[305]

The plaintiff's expert cites Ostergard, who has reviewed medical literature, and formed conclusions not based on fact, but unsubstantiated data that found its way into the medical literature.[306] Medical professionals were not attuned to the effects of the fixation process, and it was not considered in many, many instances.

Plaintiff's expert responded to work of Dr. Peter Moy of Ethicon in the following way:

> In 1985, a series of experiments, including FTIR, TEM, and histology, were performed to determine the clinical functionality of cracked sutures, the cracking mechanism, and effects of anti-oxidant concentration.[307] Dr. Moy noted that laboratory experiments had not replicated the cracking observed in explants, and proposed a systematic evaluation of explanted Prolene sutures.
>
> Response: Laboratory experiments do not replicate those from the body, as body tissue is not present for formalin fixation. It is clear that Moy and others had not realized the significance of the formalin-protein reaction, as would be the case with an explant but not with a lab originated experiment.
>
> Plaintiff's expert states, "Ethicon was also informed of the risks inherent to using polypropylene in an implantable medical device through the Material Safety Data Sheet (MSDS), which states that polypropylene is incompatible with strong oxidizers."[308] We have shown that not to be the case, as our cleaning protocol in Lewis and Batiste matters used nitric acid as one of the cleansing agents and no oxidation was noted. It is quite clear therefore Prolene is not easily oxidized given these data.

Response to the Dr. Duane Priddy Report

Plaintiff's expert pens the statement, "PP is not inert, and must be heavily stabilized with the addition of antioxidants in order to simply survive.." which is misleading. Moreover, when plaintiff's expert performed GC-MS analyses of Prolene he found only one of 5 additives, Santonox R.

For instance, Plaintiffs expert writes, "My testing in this case (gas chromatography – mass spectroscopy (GC-MS)) did not detect the presence of any of the additive other than Santonox R.[309]

- Prolene's formulation contains 5 additives.

- This disclosure by Plaintiffs expert in question any and all analytical data he has obtained, and I will respond to several of my concerns herein. It is particularly troubling in that he uses the data collected for his opinions as stated herein with respect to *in vivo* efficacy of Prolene.
- He references essentially all articles to which I have responded in this and other reports concerning this litigation, and for this reason I will not respond separately to each one.
- He, like others, reference and show SEM photomicrographs of protein-containing explants and believe them to be oxidized Prolene.

Plaintiff's expert provides a list of environmental conditions where he states it is impossible for Prolene to exist, such as:

1) high surface area exposed to oxygenated medium,
2) is under stress,
3) is in a constant warm environment, and
4) is exposed to fluids containing organics capable of extracting antioxidant stabilizers from the exposed surface.

Plaintiff's expert dismisses, however, the more than 60 successful years of Prolene suture history embodying each of his "impossible for Prolene to exist statements."

Plaintiff's expert praises and utilized two ASTM procedures for his Prolene "evaluation" and they are ASTM D3895 "Oxidative Induction Time" testing, and ASTM 1980-02, "A Standard Guide for Accelerated Aging of Sterile Medical Device Packages." Presumably he uses data from these ASTM methods from which to formulate his opinions herein. In reading the procedures, one finds the following statements taken from these ASTM methods section. I have included my response to each of the following in italics.

- The OIT is a qualitative assessment of the level (or degree) of stabilization of the material tested. *Thus, as a qualitative test no lifetime predictions, if asserted, would be unreliable.*
- The OIT measurement is an accelerated thermal-aging test and as such can be misleading. *This caution alone is sufficient for the serious scientist to seek other, more reliable methods of testing. Consideration must be given the "Transition State" and "Energy of Activation" required for chemical reactions to proceed.*
- There is no accepted sampling procedure, nor have any definitive relationships been established for comparing OIT values on field samples to those on unused products, hence the use of such values for determining life expectancy is uncertain and subjective. *This warning alone disqualifies use of these ASTM procedures for the matters at hand.*
- Volatile antioxidants may generate poor OIT results even though they may perform adequately at the intended use temperature of the finished product. *Yet, another warning not often considered, but critical. Volatile materials, at temperatures of testing, can escape the substrate rapidly and provide erroneous data.*

- This guide provides information for developing accelerated aging protocols to rapidly determine the effects, if any, due to the passage of time and environmental effects on the sterile integrity of packages and the physical properties of their component packaging materials. *These tests are designed for evaluating packaging materials, not biomaterials to be used in vivo.*

- Real-time aging protocols are not addressed in this guide; however, it is essential that real-time aging studies be performed to confirm the accelerated aging test results using the same methods of evaluation. *These test requirements have NOT been met by Plaintiffs expert.*

- To ensure that accelerated aging studies do truly represent real time effects, real time aging studies must be conducted in parallel to accelerated studies. Real time studies must be carried out to the claimed shelf life of the product. *These test requirements have NOT been met by Plaintiffs expert.*

- Accelerated aging techniques are based on the assumption that the chemical reactions involved in the deterioration of materials follow the Arrhenius reaction rate function. *Plaintiff's expert does not address this matter, thereby he cannot offer assurances for the quality of his data.*

- Care must be taken not to elevate aging temperatures solely for the shortest possible accelerated aging time. Excessively high temperatures may have an effect on the material that may never occur during real time or at room temperature (see Appendix X1). *The effect of elevated temperature on the transition state for this reaction to occur is unknown, and thus the test is completely unreliable.* Guidelines for selecting an aging temperature are as follows:

    1. Accelerated Aging Temperature (T_{AA}) should be below any material transitions or below where the package distorts. Consider the thermal transitions of the materials under investigation, for example, the choice of T_{AA} should be at least 10°C less than Tag. *The T_g of Prolene is 162^{o}C with an ASTM requirement of 10°C less than T_g. Thus, the testing temperature should be no more than 152^o C, yet Plaintiffs expert conducted his experiments at 200 ^{o}C, well out of the acceptable range of this ASTM procedure by 50^{o}C.*
    2. Keep T_{AA} at or below 60°C unless a higher temperature has been demonstrated to be appropriate. Temperatures higher than 60°C are not recommended due to the higher probability in many polymeric systems to experience nonlinear changes, such as percent crystallinity, formation of free radicals, and peroxide degradation. *The test temperature of 200 ^{o}C does not meet this ASTM requirement.*
    3. However, like all accelerated aging techniques, it must be confirmed by real time aging data. *Plaintiff's expert report is devoid of this requirement.*
- Packages and materials that have been subjected to aging, that is, accelerated and real time, must be evaluated for physical properties and integrity. *There is no evidence Plaintiffs expert accomplished this testing requirement, see immediately below.*
- Some of the physical strength properties to be considered for selection are flexure, puncture, tensile and elongation, tear, impact resistance, abrasion resistance,

yellowness index, microbial barrier (Test Method F 1608), seal strength (Test Method F 88), and burst strength (Test Methods F 1140)

- If the real-time aging results meet the acceptance criteria, then the package's shelf-life is validated. *Real time aging results have not been presented by Plaintiff's Expert and thus this testing protocol does not validate Plaintiffs expert data.*
- If the real-time aging results fail to meet the acceptance criteria, the shelf-life must be reduced to the longest shelf life for which real time testing has been successful. If product has been released to the market at risk based on the accelerated aging data, a careful review must be performed and documented, and the appropriate action taken.
- The author states, "Because of its (Prolene) poor oxidative stability, PP is generally used primarily to manufacture products that have a short service life.[310] *This statement is unfounded, has no technical support or merit. My laboratory data confirms Prolene an initial thermal degradation temperature for Prolene begins at approximately 333 ^{o}C*.
- Plaintiff's expert makes a sweeping statement that, "For example, when plastics are placed in the body, they are exposed to organic liquids (e.g., blood and fatty oils called lipids, glycerides). These chemicals act to extract the antioxidant stabilizers (very small molecules) from the long polymer chains in the plastic." *The work of Dan Burkley in his 7 year dog study proved this statement to be in error. After 7 years, physical properties of explanted sutures were significantly tougher than when implanted. Thus, physical properties of Prolene improved, rather than declined as the author would lead you to believe.*

Plaintiff's expert provides a partial chemical structure explanation of the possible free radical reactions of Prolene. And, Of course, Ethicon's antioxidants effectively retard these reactions. In attempts to explain the reactions he suggests to one not knowledgeable in chemistry, that the degradation reaction occurs at will, essentially with little to no inhibition. However, nothing could be farther from actual facts. Consider a well-known concept, the Transition State Theory, and the requirement to exceeding the Activation Energy for free radical of the transition state before free radical formation can occur,[311] and thus before any oxidative reaction can occur. Plaintiffs expert has not considered this mechanistic requirement, and until that is properly done, all comments and statements attributed to Plaintiffs expert regarding Prolene degradation is sheer supposition and not supported by basic chemical principles.

Section VII of Plaintiffs expert report is quite telling and deserves considerable attention. This section begins with the statement,

> "The PP used in Ethicon mesh is stabilized using antioxidants (e.g., Santonox R). Ethicon documentation reveals that there are additional additives added to the Prolene resin, including Calcium Stearate, Dilaurylthiodipropionate (DLTDP), Procol LA-10, and CPC Pigment 22. My testing in this case (gas chromatography – mass spectroscopy (GC-MS)) did not detect the presence of any of the additive other than Santonox R."

First, in setting the record correctly, Prolene is formed only after all five required additives are added to PP and extruded. Thus, Prolene, in fact, does contain ingredients the author says his testing could not identify. It is obvious therefore, that Plaintiffs expert has offered incorrect opinions based on erroneous data.

Plaintiff's expert offers Figure 1, a SEM photomicrograph taken from Henri Clavé, as have others to which I have responded.[312]

Plaintiff's expert Summary and conclusions are not supported by existing, high quality science. Likewise Plaintiffs expert continues to discuss PP (polypropylene) rather than Prolene. I have responded to his summary and conclusions in italics, i.e.

- He states, "In order to fabricate a mesh, the PP polymer chains must be short." *The term "short" is not a term of art when discussing polymer science. It is a relative term and has no meaning herein.*
- He states, "PP mesh will rapidly lose its strength as the polymer chains disentangle when the mesh is placed under mechanical stress." *Tensile strength, elongation and modulus values for Prolene establish the polymer as a high performance thermoplastic.*
- He states, " The PP is inherently oxidatively unstable compared with other plastics (because of the tertiary bonded hydrogen) forcing the addition of high levels of antioxidant stabilizers to be added to the PP to allow it to be stable enough to be fabricated into mesh without material degradation." *His statement defies reality given the annual product in the U.S. is approximately 8.4 million metric tons, and 52.2 metric tons worldwide.*
- He states, "The antioxidants are depleted by migration from the mesh and by oxidation as they do their job to protect the PP against degradation." *Plaintiff's expert has not provided reliable information to affirm his belief. Ethicon's Dan Burkley managed a long-term scientific study and collected laboratory data confirming exemplary antioxidant protection provided by Santonox R and DLTDP to Prolene during a 7 year in vivo period. Prolene's physical properties did not diminish over the 7 year period, but instead improved rather dramatically.*
- He states, "Oxygenated liquids (e.g., blood, lipids and glycerides) present in body tissue extract antioxidants from the surface of PP allowing rapid degradation and embrittlement of the surface of the mesh fibers*." Plaintiff expert again offers no quantifiable data to his claims, and does not consider the Burkley study, yet his writings are in strict contradiction to Prolene's performance.*
- Plaintiffs expert refers to the work of Dr. Jimmy Mays, yet he did not mention or is unaware that Dr. Mays did not use Ethicon's Prolene, but a Boston Scientific product.
- Plaintiff's expert's Section **X includes** "the essence of any accelerated aging methodology begins with an understanding of the stresses applied to the polymer during service, and how those stresses may affect aging properties." He continues by writing, "Some typical polymeric stressors include thermal, oxidative, chemical, and physical stresses." *Surely he understands his teachings defeat his data collected according to ASTM tests F1980 and D-3895. Plaintiff's expert analytical techniques require 200 ^{o}C (392 ^{o} F). He has not, however, given an explanation as to how this greatly elevated temperature may affect aging properties of Prolene.*
- Plaintiff's expert speaks of embrittlement of Prolene. *He has offered no scientific data to affirm this precept, and neither has he suggested how to measure or test for embrittlement.*

- Plaintiffs expert states, "Therefore the OIT data is a best case situation because the only mechanism for loss of antioxidant during the OIT tests is chemical reaction; i.e., loss by migration into body fluids is not taken into account." *Plaintiff's expert completely dismisses loss by excessive heating, a stressor he has identified*.
- Plaintiff's expert refers to liquid chromatography data supposedly confirming the gradual decrease in Oxygen Induction Time as being due to migration of antioxidant to the surrounding medium. *Plaintiff's expert could only detect one of five known Prolene additives via his GC-MS technique. He also fails to include the following comments from the authors of work cited[313] i.e. " The large scatter in the data makes an accurate assessment of the activation energy impossible" and "The low boundary loss rate makes the assessment of the antioxidant diffusivity far from ideal and it is associated with a sizeable uncertainty." In other words the authors of the cited article candidly reveal their technique is not quantitative nor precise-yet this is a technique Plaintiffs expert has cited and used for data collection in this matter. Note the authors of the cited article state -the activation energy of the Transition State Theory cannot be accurately assessed by their methods.*

Section XI of Plaintiff expert report discusses data collection from 10 Ethicon mesh samples extracted with methylene chloride and analyzed by GC-MS to identify and quantify the relative amount of Santonox R present in the mesh samples. *If the GC-MS spectroscopy technique and/or instrumentation used by Plaintiffs expert could identify only one of five Prolene formulation additives, little to no confidence can be attributed to his data.*

Plaintiff's expert report **Section XII** includes discussion of explants provided by Dr. Robert Guidoin to Ethicon employees. First and foremost, the explants were evaluated in their "as is" state. While there is suggestion that some of the explants may have been subjected to a bleach treatment, it is Dr. Guidoin[314] who coauthored a manuscript on the difficulty in cleaning explants, more often than not requiring strong chemicals.

Plaintiff's expert **Section XIII. Expert Opinion** includes lack of reliable data and unsupported opinions to which I am in total disagreement. None of his opinions are supported in any way by reliable and believable scientific data. Consider as one example the following:

Priddy – Oxygen Induction Time Data for Gynemesh Explants

	OIT-MINUTES	ISOT-MINUTES
Sample 1.	42.4	35.0
Sample 2.	38.4	34.0
Sample 3.	32.6	21.0
Sample 4.	23.2	19.2
Sample 5	18.6	16.4
Sample 6	31.8	29.00

These data are in conjunction with his writings, "that Over 150% variance was found between the 10 exemplar samples," while his reported data for Gynemesh exemplars showed greater than 100% variance. Whether you take the exemplar or explant data, it is very clear that the test

methods he has employed lack the sophistication to provide meaningful values from which one can draw valid conclusions.

Response to the Dr. Scott Guelcher Report

Guelcher Summary of Opinions followed by Response

1) Polypropylene (PP) reacts with molecular oxygen by autoxidation outside the body at elevated temperatures, resulting in chain scission and deterioration in its mechanical properties.

Response: Of course, however our analytical work has confirmed thermal degradation for Prolene in an oxygen atmosphere begins at approximately 333 ^{o}C.

2) After implantation in the body, polypropylene reacts with reactive oxygen species secreted by inflammatory cells, resulting in oxidation, chain scission and mesh embrittlement.

Response: Liebert, who is cited by Guelcher, estimated the induction time for PP oxidation under *in vivo* conditions (37^{o} C in 3.3% O_2) is approximately 20 years. He followed with data that did not support his opinion. His opinions were dependent upon carbonyl group formation and positive proof of PP oxidation. However, PP oxidation hasn't been proven since no carbonyl groups have been clearly identified. Furthermore, oxidation, as alleged by Guelcher, results in chain scission, molecular weight loss, and loss of toughness. None of these properties have been confirmed.

3) The dynamic environment where the polypropylene mesh is implanted coupled with the foreign body reaction leads to oxidation, chain scission, reduction in molecular weight, embrittlement, degradation, flaking, pitting, and cracking.

Response: Oxidation produces Carbonyl Index and there is no proof this has occurred. Fayolle[315] and particularly George Wypych[316] show this, i.e. you cannot have oxidation and loss of molecular weight without carbonyl group formation.

4) The human body does not stop responding to an implanted mesh, or any frayed particles of mesh released during implantation, unless the product is removed in its entirety;

Response: Significant data exists proving proteins rush to the surface when a foreign body is implanted.[317,318,319] The proteins (Collagen) immediately adsorb strongly to PP and, as such, are difficult to remove, as others agree.[320] We have shown this by our own experiments. See Appendix R1 (SEM, FTIR, LM).[321] The adsorbed protein layer coats the explant surface and "protects" it such that other body cells do not "see" PP as a foreign object, they only "see" adsorbed proteins.